

Exhibit 195

REDACTED

**UNITED STATES DISTRICT COURT
DISTRICT COURT OF NEW JERSEY**

IN RE: VALSARTAN PRODUCTS LIABILITY
LITIGATION

Case No. 1:19-MD-2875-rbk

Expert Report of William J. Lambert, Ph.D.

RESTRICTED CONFIDENTIAL

SUBJECT TO PROTECTIVE ORDER

REDACTED

I. Introduction

1. I submit this report in regard to In Re Valsartan, Losartan, and Irbesartan Products Liability Litigation, No. 1:19-md-2875-RBK. This report is made on behalf of Aurobindo Pharma Ltd., Aurobindo Pharma USA, Inc., and Aurolife Pharma LLC.
2. This report presents my analyses and opinions based on my education, training, and experience and the materials I have considered, which are listed in the footnotes of this report and/or are included in documents listed in Appendix A.
3. All of my opinions are made to a reasonable degree of professional certainty.
4. I reserve the right to modify or supplement this report if and when appropriate, particularly based upon additional information, data, documents, or other evidence, of which I am made aware subsequently. I expressly reserve my right to supplement or modify my opinions expressed herein.

II. Background and Experience

5. Appendix B to this report is my current *curriculum vitae*. A summary of my educational and professional background is provided below.
6. I received a Bachelor of Science in Pharmacy from the University of Rhode Island in 1981. After completing my undergraduate studies, I began graduate studies under Distinguished Professor William Higuchi in Pharmaceutical Chemistry at the University of Michigan in 1981 and the University of Utah from 1982-1986 where I received my Ph.D. in Pharmaceutics.
7. After the University of Utah, I gained industry experience working as a Scientist and Research Scientist in drug delivery research and development at The Upjohn Company from 1987-1991. I then worked at Pfizer Central Research from 1991 to 1997 as a Senior Research Scientist/Senior Research Investigator, where I was responsible for managing a scientific group developing a variety of different pharmaceutical products.

8. I worked at Eisai Inc. starting in 1997, where I began as Director of Product Development in Pharmaceutical and Analytical Research and Development. In this role, I was responsible for starting up, maintaining, validating, and scheduling a functional cGMP manufacturing facility, which supplied drug products worldwide. This facility underwent a successful FDA inspection within only two years of construction. In this role, I also provided technical support for United States regulatory filings. In 2004, I was promoted to Senior Director of Drug Delivery Technology in Pharmaceutical and Analytical Research and Development.
9. From 2006 to 2011, I worked at Pacira Pharmaceuticals, Inc. as Senior Vice President of Pharmaceutical Development, where I reported directly to the CEO and President of Pacira and led teams developing various protein, peptide and small molecule therapeutics in the areas of formulation, analytical, clinical supply manufacture, scale-up, technology transfer, CMC and preclinical regulatory filings, and manufacturing technical support. Pacira had three cGMP aseptic manufacturing areas used for commercial and clinical products. In this role, I successfully filed the CMC and preclinical sections of an IND and IMPD for Pacira's lead internal Phase 2/3 program and successfully scaled up a complex formulation process for Pacira's pharmaceutical drug product, Exparel®. I also hosted cGMP audits of our facilities by partner companies.
10. From 2011 to 2015, I worked at MedImmune as Fellow and Head of the Innovative Drug Delivery Group, where I was responsible for identifying, assessing and developing drug delivery technologies for use with MedImmune protein and peptide drugs and vaccines, which included formulation and device-based technologies. In this role I participated in several due diligence exercises related to in-licensing of products and their cGMP production.
11. From 2015 to 2018, I worked at Omeros Corporation as Vice President of Chemistry, Manufacturing, and Controls, where I was responsible for all aspects of chemistry, manufacturing, and controls of Omeros's drug substances and drug products from development

through and including manufacturing. In this role, I led formulation, process, and analytical development, manufacturing, logistics supply chain management, and quality control for both biological and chemical drug substances and products, and oversaw all CMC-related regulatory reports and submissions. This included working closely with several cGMP drug substance and drug product contract manufacturing organizations (CMOs). All cGMP work at Omeros was performed by CMOs. My group, in collaboration with Omeros' QA group, led the selection, management, and review of these CMOs and their work.

12. In 2018 I founded Module 3 Pharmaceutical Consulting, where I am currently a Pharmaceutical Development, CMC, cGMP, and Drug Delivery Consultant. I provide expert consultation in the CMC sections of regulatory filings for INDs, IMPDs, NDAs, and BLAs. I also conduct due diligence assessments of pharmaceutical products, manufacturing facilities, drug delivery technologies, and regulatory filings and provide consulting services regarding product development and manufacture including cGMPs.
13. During my career, I have authored or co-authored over 30 peer-reviewed articles and have given over 30 presentations. I am also on the Editorial Advisory Board of the Journal of Pharmaceutical Sciences and the Advisory Board for the Handbook of Pharmaceutical Excipients (2002-present).
14. In total, I have 35 years of experience with the manufacturing process for drug substances and drug products. This experience includes direct and extensive involvement with manufacturing cleaning procedures. I also have direct and extensive knowledge of and experience with Current Good Manufacturing Practices (cGMPs). One example of my experience with cGMPs relates to process controls used in aseptic manufacturing. I led the effort at Eisai's Research Triangle Park ("RTP") facility to put aseptic process validation in place at that facility. A second example relates to cleaning verification and validation of manufacturing equipment. I authored the

Standard Operating Procedure used at Eisai RTP to ensure that residues from one batch did not contaminate a subsequent batch.

III. Fees and Prior Testimony

15. In the past four years, I have provided no deposition or trial testimony.
16. Retaining counsel is being billed at \$600 per hour for consulting, and \$750 per hour for deposition and testimony, by the expert witness search and placement firm, ExpertConnect Litigation Support, LLC, who placed me on this matter and is responsible for all billing for my services. I (Dr. William Lambert) retain 53.8% of that hourly rate for consulting, and 66.66% of that hourly rate for deposition and testimony for my expert services. No part of this compensation is dependent on my opinions, conclusions, or determinations given, or on the outcome of this case.

IV. Summary of My Opinions

17. In addition to those opinions discussed below, a summary of my opinions are as follows:
- i) The Aurobindo VCDs met the USP compendial standards at the time, were approved AB generics listed in the Orange Book, and were bioequivalent to their respective RLDs.
 - ii) Plaintiffs' experts failed to apply the correct standards for bioequivalence and pharmaceutical equivalence and did not identify any evidence that the presence of nitrosamines altered bioequivalence.
 - iii) The presence of nitrosamines in certain lots of Aurobindo's VCDs did not change bioequivalence, and all Aurobindo VCDs were not "worthless."
 - iv) Aurobindo appropriately and reasonably investigated the presence of nitrosamines once they were detected in certain lots. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] This shows that the impurities were intermittent, were at very trace levels when they occurred, and were not introduced as part of the valsartan synthetic route at Aurobindo.

- v) Aurobindo had no reason to test specifically for nitrosamines in its API, as their presence was unknown and unexpected and not identified in the USP. Established test methods at the time would not have detected the presence of nitrosamines. Aurobindo had no reason to utilize Gas chromatography-mass spectrometry (GC-MS) prior to the time nitrosamines were detected in its VCDs. FDA did not publish a GC/MS method for NDMA and NDEA until 12/11/2018 and a Liquid Chromatography-mass spectrometry (LC-MS) method until 05/21/2019.
- vi) Aurobindo prepared a reasonable and appropriate risk assessment for the formation of nitrosamines in the synthesis of valsartan, and it competently investigated its VCDs for nitrosamines.
- vii) The FDA's Orange Book did not constitute or create manufacturer warranties.
- viii) Contract manufacturing is widely used in the pharmaceutical industry, and the use of non-dedicated equipment is permitted by the FDA and is common. Reduced testing also is appropriate once a vendor is qualified.
- ix) Aurobindo reasonably qualified and oversaw Lantech.
- x) The use of recovered solvents is customary in the industry, is allowed by the FDA, and environmentally appropriate.

xi) The types of CGMP Compliance issues observed by the FDA and related to the manufacture of VCDs are not the types of compliance issues that would impact all Defendants' VCDs equally. Each manufacturer is independent, with different quality systems, different scientists and managers, different facilities, different equipment, different data, different personnel, different vendors, and different processes and procedures.

V. Aurobindo Valsartan Containing Drugs (VCDs) and Nitrosamines

18. **Valsartan.** Valsartan is an angiotensin II receptor blocker (ARB) and is indicated for hypertension, heart failure, and post-myocardial infarction (package insert for branded Valsartan, Diovan). Diovan is the Reference Listed Drug (RLD) for Aurobindo's valsartan tablets.
19. Aurobindo has four approved ANDAs for VCDs in the USA: (1) valsartan; (2) amlodipine besylate and valsartan; (3) amlodipine besylate, valsartan, and hydrochlorothiazide; and (4) valsartan and hydrochlorothiazide (Orange Book). The Orange Book lists these four VCDs as therapeutically equivalent (AB rating) to the respective brand-name products: Diovan; Exforge; Exforge HCT; and Diovan HCT.
20. **Nitrosamines.** Beginning in 2018, nitrosamine impurities were unexpectedly found in a number of drugs including some angiotensin II receptor blockers (ARBs), ranitidine, nizatidine, and metformin (FDA, Control of Nitrosamine Impurities in Human Drugs Guidance for Industry, <https://www.fda.gov/media/141720/download>). FDA issued guidance to manufacturers on this subject in September 2020. The FDA also has provided guidance to patients whose medications may contain nitrosamines (FDA, Information about Nitrosamine Impurities in Medications, <https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications>). FDA notes that "Nitrosamines are common in water and foods, including cured and grilled meats, dairy products and vegetables. Everyone is exposed to some level of nitrosamines." FDA has set acceptable daily intake limits for nitrosamines. If drugs

contain levels of nitrosamines above the acceptable daily intake limits, FDA recommends these drugs be recalled by the manufacturer as appropriate.

21. The determination of acceptable intake (AI) limits by the FDA is described in the FDA Guidance titled Control of Nitrosamine Impurities in Human Drugs and follows the procedures in ICH M7.

22. N-Nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA) are two nitrosamines.

FDA's acceptable intake limits of NDMA and NDEA in drug products as 96 and 26.5 nanograms/day, respectively (Control of Nitrosamine Impurities in Human Drugs Guidance for Industry). A nanogram is one billionth of a gram or 10^{-9} g.

23. **Recalls.** No lots of Aurobindo valsartan have been recalled due to the presence of NDMA. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

24. **New specification and process for the US.** [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]. This is more conservative than the FDA's AI limit. [REDACTED]

[REDACTED] These voluntary changes pre-date the FDA's nitrosamine guidance.

25. The FDA has advised "Health care professionals should continue to prescribe medications when clinically appropriate even though they may have low levels of nitrosamine impurities." (FDA, Information about Nitrosamine Impurities in Medication, <https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications>). Thus, the FDA has assessed the risk of nitrosamines at levels below the AI to the benefit that drugs like valsartan provide to the patient, determining that the benefits outweigh the risks.

VI. Overview of cGMPs

26. cGMP refers to the Current Good Manufacturing Practice regulations enforced by the FDA. (FDA, Facts About the Current Good Manufacturing Practices (CGMPs), <https://www.fda.gov/drugs/pharmaceutical-quality-resources/facts-about-current-good-manufacturing-practices-cgmps>). cGMPs provide for systems that assure proper design, monitoring, and control of manufacturing processes and facilities. Adherence to the cGMP regulations assures the identity, strength, quality, and purity of drug products by requiring that manufacturers of medications adequately control manufacturing operations. This includes establishing strong quality management systems, obtaining appropriate quality raw materials, establishing robust operating procedures, detecting and investigating product quality deviations, and maintaining reliable testing laboratories. This formal system of controls at a pharmaceutical company, if adequately put into practice, helps to prevent instances of contamination, mix-ups, deviations, failures, and errors. This assures that drug products meet

their quality standards. These regulations are called “current” GMPs because they can evolve overtime.

27. According to the FDA, during a cGMP inspection, “investigators may observe conditions they deem to be objectionable. These observations, are listed on an FDA Form 483 when, in an investigator’s judgment, the observed conditions or practices indicate that an FDA-regulated product may be in violation of FDA’s requirements.” (FDA, Inspection Observations, <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/inspection-observations>). The Form 483 is provided to the manufacturing firm’s management at the end of the inspection. “Companies are encouraged to respond to the FDA Form 483 in writing with their corrective action plan and then implement that corrective action plan expeditiously.” (FDA, FDA Form 483 Frequently Asked Questions, <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/fda-form-483-frequently-asked-questions>).
28. In my experience, firms will generally provide the FDA with their corrective action plan in response to an inspection and Form 483.
29. Observations can be subjective to some degree and are intended to identify conditions or practices that “may be in violation of FDA’s requirements.” (FDA, Inspection Observations, <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/inspection-observations>). Observations do not constitute a final agency determination that any condition is in violation of the Food, Drug & Cosmetic Act or related regulations. The observations may or may not be well-founded, but they trigger a discussion and/or response that addresses the observations.

VII. My Opinion of Statements in the Third-Party Payors’ Brief in Support of Motion to Certify Class

30. The motion states that “Defendants’ generic VCDs (1) were, in fact, not U.S. Food and Drug Administration (‘FDA’) approved generic versions of these drugs, (2) did not meet the quality standards or match the ingredients listed on their labels and package inserts, (3) did not satisfy the criteria to be accurately described as generic equivalents, and (4) did not meet the applicable USP and Orange Book standards, but instead (5) were of a lesser quality and were adulterated and/or misbranded (and thereby rendered worthless) by contamination with EPA-listed probable human carcinogens known as N-nitrosodimethylamine (‘NDMA’) and N-nitrosodiethylamine (‘NDEA’).” (Third-Party Payors’ Brief in Support of Motion to Certify Class at 2, D.E. 1749 at 8.).

31. The above statements are not factually correct. As discussed in more detail below, a generic drug and a reference listed drug are considered bioequivalent if they have an equivalent rate and extent of absorption. The Aurobindo VCDs, including those with trace nitrosamine, were bioequivalent to the reference listed drug (RLD). There is no evidence to the contrary. In addition, as per FDA’s Orange Book, these products were and are AB approved generics. They were bioequivalent and did match the label and package insert. They did satisfy the criteria to be accurately described as generic equivalents and did meet the applicable USP and Orange Book standards at the time. They could perform their intended purpose and were not worthless, and in fact the FDA advised “Health care professionals should continue to prescribe medications when clinically appropriate even though they may have low levels of nitrosamine impurities.”

(FDA, Information about Nitrosamine Impurities in Medications,

<https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications>). As shown by testing of Aurobindo’s lots, [REDACTED]

[REDACTED]

[REDACTED]

32. It is common when a manufacturer is inspected by the FDA for the inspector to file a Form 483 with various observations, suggesting that a site may be out of compliance. These inspections are not unlike home inspections performed when one is about to purchase a house. It is rare to have no observations. For example, deviating from a company SOP is non-compliance. All SOPs do not, however, have an equivalent impact on manufacturing. According to the FDA database, just in 2020 there were 349 drug 483s (each 483 would have one to dozens of observations), which shows that 483s commonly occur. But that does not necessarily render all products manufactured at all sites receiving a Form 483 unusable and thus worthless. Rather, it means that the products and manufacturer(s) may be subject to regulatory action. One still must look at the specific observations at the manufacturing site, the effect on the products, and whether the products were nonetheless therapeutically equivalent.
33. In addition, there were 182 drug-related warning letters in 2020. One of these warning letters for adulterated drug product was sent to a very recognizable company; Pfizer (Pfizer Healthcare India Private Limited). In 2018, the Pfizer site in McPherson, KS received a 483 with 8 observations. That did not mean that every Pfizer drug product manufactured at the site became “worthless.”

VIII. My Opinion of Statements in the Expert Report of Kali Panagos, Pharm.D., R.Ph.

34. Overall, the statements by Dr. Panagos are very general in nature and do not appear to be based on any actual data, particularly in regard to Aurobindo API or drug product.
35. **Orange Book.** Dr. Panagos references the Orange Book regarding Pharmaceutical Equivalents and “AB” ratings.
36. The official title of the Orange Book is APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS.
37. The MARCH 20, 2020 EDITION of the Orange Book states the following:

(1) Drug products that FDA considers to be therapeutically equivalent to other pharmaceutically equivalent products, i.e., drug products for which:

(a) there are no known or suspected bioequivalence problems. These are designated

AA, AN, AO, AP, or AT, depending on the dosage form; or

(b) actual or potential bioequivalence problems have been resolved with adequate in vivo and/or in vitro evidence supporting bioequivalence. These are designated **AB**.

38. Dr. Panagos states the “AB” rating in the FDA Orange Book, based as it is on the generic drug manufacturer’s ANDA, represents a manufacturer’s warranty to TPPs and P&T Committees for placement on a prescription drug formulary. Dr. Panagos also states that “The warranty from manufacturers for these products turned out to false.” (Expert Report of Kali Panagos, Pharm.D., R.Ph., at 10, D.E. 1749-3 at 12). This is incorrect. The FDA Orange Book does not create, and is not understood to be, a manufacturer’s warranty and instead represents FDA approvals based on its review of ANDAs.

39. **ASHP (American Society of Health-System Pharmacists) Guidance.** Dr. Panagos references an ASHP guidance (ASHP Guidelines on the Pharmacy and Therapeutics Committee and the Formulary System, <https://www.ashp.org/-/media/assets/policy-guidelines/docs/guidelines/gdl-pharmacy-therapeutics-committeeformulary-system.ashx>). The guidance is for hospital Pharmacy and Therapeutics (P&T) committees (who decide what drugs go on a formulary). That guidance does not and cannot render the FDA Orange Book a manufacturer’s warranty. ASHP is a professional organization for pharmacists, and not manufacturers.

40. **Bioequivalence.** Dr. Panagos states the “presence of the contaminant rendered the manufacturer defendants’ versions of VCDs not equivalent to the branded product as indicated in the Orange Book which serves as the source of truth for bioequivalence.” (Expert Report of

Kali Panagos, Pharm.D., R.Ph., at 9, D.E. 1749-3 at 11). Dr. Panagos did not apply the correct standard for bioequivalence.

41. Bioequivalence (BE) is defined in the Orange book (and CFR) as:

(1) *Bioequivalence*. Bioequivalence is the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study. Section 505(j)(8)(B) of the FD&C Act describes certain conditions under which a test drug and reference listed drug (see Section 1.4) shall be considered bioequivalent:

- (a) (i) the rate and extent of absorption of the [test] drug do not show a significant difference from the rate and extent of absorption of the [reference] listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses; or
- (b) (ii) the extent of absorption of the [test] drug does not show a significant difference from the extent of absorption of the [reference] listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the [reference] listed drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.

(Orange Book Preface, <https://www.fda.gov/drugs/development-approval-process-drugs/orange-book-preface>) (alterations in original).

42. In my opinion, the bioequivalence statement of Dr. Panagos lacks a scientific basis. There is no credible mechanism for nitrosamines to affect bioequivalence. [REDACTED]

[REDACTED]

The rate and extent to which the active ingredient or active moiety in these products becomes available was not impacted by these low levels of NDMA or NDEA, and I am unaware of any evidence that it was impacted.

43. Furthermore, the presence of a nitrosamine in and of itself is not grounds for recalling the drug product or discontinuing its use. In fact, by virtue of its guidance setting what FDA determines to be acceptable intake limits, FDA has recognized that the presence of nitrosamines, at some levels, is in fact acceptable. (FDA, Information about Nitrosamine Impurities in Medications, <https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications>; FDA, Control of Nitrosamine Impurities in Human Drugs, Guidance for Industry, <https://www.fda.gov/media/141720/download>).

44. Other impurities are also allowed in drug products up to a stated limit. For example, ICH Q3D, Elemental Impurities, provides an illustrative example where lead is allowable up to 2 mcg/gm.

45. Finally, the FDA advises “Patients taking prescription medications with potential nitrosamine impurities should not stop taking their medications.” (FDA, Information about Nitrosamine Impurities in Medications, <https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications>). In my experience, this advice represents a risk-benefit analysis by FDA and its determination that that these products still provide their therapeutic action, which far outweigh the risk from very low levels of nitrosamine.

46. The FDA defines RLD (Reference Listed Drug) as follows: “A Reference Listed Drug (RLD) is an approved drug product to which new generic versions are compared to show that they are bioequivalent. A drug company seeking approval to market a generic equivalent must refer to

the Reference Listed Drug in its Abbreviated New Drug Application (ANDA). By designating a single reference listed drug as the standard to which all generic versions must be shown to be bioequivalent, FDA hopes to avoid possible significant variations among generic drugs and their brand name counterpart.” (FDA, Drugs@FDA Glossary of Terms, <https://www.fda.gov/drugs/drug-approvals-and-databases/drugsfda-glossary-terms#R>).

47. In the declaration, Dr. Panagos uses the terms same and identical several times. It should be noted that even for the Reference Listed Drug (RLD) manufacturer, one lot may differ from the next, and levels of impurities in drug substance lots may vary from each other. This is true whether one is discussing a RLD or a generic. There is typically some level of impurities, and in fact, ICH Q3A, Impurities in New Drug Substances, the reporting threshold for impurities in API is 0.05% for drugs with a daily dose of up to 2 grams per day. Impurities below the reporting threshold are not reported in regulatory filings.
48. The FDA Fact Sheet on Generic Drugs recognizes that there may be differences between the RLD and the generic. “Some differences, which must be shown to have no effect on how the drug functions, are allowed between the generic and the brand. Generic drug manufacturers must submit evidence that all ingredients used in their products are safe, and FDA must review that evidence.” (FDA, FDA Fact Sheet, What’s Involved in Reviewing and Approving Generic Drug Applications?, <https://www.fda.gov/media/99163/download>).

IX. My Opinion of Statements in Plaintiffs’ Memorandum of Law in Support of Their Motion for Class

Certification of Consumer Economic Loss Claims

49. **Non-dedicated equipment.** The above Memorandum states [REDACTED]
- [REDACTED]
- [REDACTED] and [REDACTED]
- [REDACTED]

[REDACTED] (Plaintiffs'

Memorandum of Law in Support of Their Motion for Class Certification of Consumer Economic Loss Claims at 32–33).

50. In my experience, the use of non-dedicated equipment is permitted by the FDA and customary in the industry.

51. Contract manufacturing is widely used in the pharmaceutical industry. Contract manufacturing, particularly for API, routinely uses non-dedicated equipment. Contract manufacturers tend to discourage the use of dedicated equipment because it functions as a limit on their ability to manufacture for other customers inasmuch as many APIs are manufactured infrequently (e.g., once per year).

53. There are a number of reasons why non-dedicated equipment is used. Stainless steel tanks are generally custom made and have large footprints, taking up significant area within a room or facility. Each facility has a finite square footage, and thus, cannot add equipment indefinitely.

54. **Cleaning process.** The Memorandum suggests that [REDACTED]
[REDACTED] (Plaintiffs' Memorandum of Law in Support of
Their Motion for Class Certification of Consumer Economic Loss Claims at 32).

55. Aurobindo did take appropriate actions in regard to auditing Lantech, and providing Lantech with observations so as to make improvements to Lantech's processes. [REDACTED]

[REDACTED]

[REDACTED] It is common for audits of vendors to have multiple observations. Their oversight of Lantech was consistent with industry practices.

56. The validation of cleaning processes is discussed in FDA's Guide to Inspections Validation of Cleaning Processes (7/93). This document notes that the "FDA does not intend to set acceptance specifications or methods for determining whether a cleaning process is validated." (FDA, Guide

to Inspections Validation of Cleaning Processes, <https://www.fda.gov/validation-cleaning-processes-793>).

57. One of the most common methods of setting acceptance limits in the industry is based on the Maximum Allowable Carryover (MAC) approach (Cleaning Validation for the 21st Century: Acceptance Limits for Active Pharmaceutical Ingredients (APIs): Part I., A. Walsh, Pharm. Eng., July/Aug 2011, pp. 74-83).

58. The MAC approach is clearly focused on the drug that needs to be cleaned from the equipment. Trace impurities are generally not considered because they are insignificant compared to the active drug in the equipment.

59. [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED] In my experience, this shows that the impurities were intermittent, were at very trace levels when they did occur, and were not introduced as part of the valsartan synthetic route at Aurobindo.

60. **Reduced testing.** The above Memorandum states [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]

[REDACTED] (Plaintiffs'

Memorandum of Law in Support of Their Motion for Class Certification of Consumer Economic Loss Claims at 34).

61. What is described here is a recognized and acceptable industry practice and reflects the testing performed commonly by manufacturers as per their standard operating procedures (SOPs), under certain conditions. Initially, there is typically full testing of each batch to verify that the material meets the testing conducted by the vendor. Once the testing verifies that the material meets specs for a given number of batches, the manufacturer conducts less frequent testing. The vendor continues to test each batch and issues a Certificate of Analysis (CoA).
62. Reduced testing is a reasonable and customary approach once a vendor is qualified and eliminates unnecessary testing. Once the vendor's material is determined to consistently meet specifications, reduced testing is appropriate.
63. Importantly, testing against the CoA was unlikely to detect an unexpected trace impurity such as NDMA and NDEA. In general, the assays that support the CoA will only detect impurities if they are designed to detect those specific impurities. This is particularly true when one considers the extremely low levels of nitrosamines at issue here. Thus, even if Aurobindo conducted more extensive testing using customary methods that duplicated the testing for the CoA, that additional testing would not have detected NDEA or NDMA.
64. Aurobindo had no reason to test specifically for nitrosamines in the API, as their presence was unknown and unexpected. Standard tests would not have detected the presence of nitrosamines. From PF Online, published September 1, 2020: "The AIs (acceptable intake) associated with nitrosamines require the application of sensitive analytical procedures." (United States Pharmacopeia, General Chapter 1469 Nitrosamines Impurities).

65. FDA's ICH Q7A has a provision for Sampling and Testing of Incoming Production Materials. "At least one test to verify the identity of each batch of material should be conducted, with the exception of the materials described below. A supplier's certificate of analysis can be used in place of performing other tests, provided that the manufacturer has a system in place to evaluate suppliers. Supplier approval should include an evaluation that provides adequate evidence (e.g., past quality history) that the manufacturer can consistently provide material meeting specifications. Complete analyses should be conducted on at least three batches before reducing in-house testing. However, as a minimum, a complete analysis should be performed at appropriate intervals and compared with the certificates of analysis. Reliability of certificates of analysis should be checked at regular intervals." (FDA, Guidance for Industry, Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-q7a-good-manufacturing-practice-guidance-active-pharmaceutical-ingredients>). Processing aids, hazardous or highly toxic raw materials, other special materials, or materials transferred to another unit within the company's control do not need to be tested if the manufacturer's certificate of analysis is obtained, showing that these raw materials conform to established specifications." (*Id.*).

66. **Residual Solvent.** The above Memorandum states [REDACTED]. (Plaintiffs' Memorandum of Law in Support of Their Motion for Class Certification of Consumer Economic Loss Claims at 34–35).

67. [REDACTED]
[REDACTED]
[REDACTED]

68. The statement that the Memorandum makes, [REDACTED]

(Plaintiffs' Memorandum of Law in Support of Their Motion for Class Certification of Consumer Economic Loss Claims at 34) is simply inaccurate. Residual solvent testing addresses levels of residual solvents and does not test for impurities that may have been in the solvent.

69. **Synthetic mechanism.** The above Memorandum states [REDACTED]

[REDACTED] (Plaintiffs' Memorandum of Law in Support of Their Motion for Class Certification of Consumer Economic Loss Claims at 36).

70. Assessing the synthetic mechanism is a reasonable and customary approach and complies with applicable industry standards. A Working Group in the International Consortium for Innovation and Quality in Pharmaceutical Development explained that ICH M7 Option 4 allows the utilization of process knowledge to reduce analytical testing without any compromise on patient safety. (Borths et al., Control of Mutagenic Impurities: Survey of Pharmaceutical Company Practices and a Proposed Framework for Industry Alignment, Org. Process Res. Dev., 2021, 25,4, 831-837). This is discussed in more detail below.

71. **Gas chromatography-mass spectrometry (GC-MS).** The Memorandum goes on to state

[REDACTED]
[REDACTED] (Plaintiffs' Memorandum of Law in Support of Their Motion for Class Certification of Consumer Economic Loss Claims at 36). GC-MS was not recommended for use until NDEA and NDMA were detected in 2018.

72. FDA did not publish a GC/MS method for NDMA and NDEA until 12/11/2018, another GC-MS method until 1/28/2019, and a Liquid Chromatography-mass spectrometry (LC-MS) method until 05/21/2019. (https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan/?utm_campaign=UPDATE%20on%20angiotensin%20II%20receptor%20blocker%20%28

[ARB%29%20recalls%20-%20FDA%20publishes%20LC-HRMS%20and%20RapidFire-](#)

[MS%2FMS&utm_medium=email&utm_source=Eloqua#testingmethods">MS%2FMS&utm_medium=email&utm_source=Eloqua#testingmethods](#)). The relevant testing by

Aurobindo predated these publications.

73. Pharmacopeial Forum (PF) is an online journal in which the USP publishes proposed revisions to USP–NF for public review and comment.

74. From PF Online, published September 1, 2020: “The AIs (acceptable intake) associated with nitrosamines require the application of sensitive analytical procedures. In many cases, the most reliable procedures take advantage of the sensitivity and selectivity of chromatographic separation techniques coupled with quantitation by mass spectrometry (e.g., [High Performance Liquid Chromatography-MS/MS] (HPLC–MS/MS) and GC–MS/MS).” (United States Pharmacopeia, General Chapter 1469 Nitrosamines Impurities). MS/MS is referred to as tandem mass spectrometry where two or more mass analyzers are coupled together.

75. The date of PF publication is nearly two years after [REDACTED] Aurobindo acted reasonably, timely, and appropriately in modifying its test method for nitrosamines.

76. To detect NDEA, a very sensitive method is required because of the very low levels of nitrosamine.

77. **Drug Product Specifications and Test Methods.** HPLC with ultraviolet (UV) spectroscopic detection, not MS, is a generally accepted analytical technique for testing drug products. (Mahesh Patil, Different Types of HPLC Detectors, <https://chrominfo.blogspot.com/2020/07/different-types-of-hplc-detectors.html>).

78. The test methods used by Aurobindo for valsartan content and related substances in valsartan tablets were [REDACTED] The specifications approved by the FDA (and consistent with the valsartan tablet USP monograph) include [REDACTED]

[REDACTED]

79. USP requirements (USP-NF - Valsartan Tablets - Official Date: 31-Dec-2012) applied to the valsartan lots, including those containing NDMA and NDEA impurities. These requirements included testing for identity of the API, dissolution testing, an assay showing 95.0 to 105.0% valsartan relative to a USP reference, individual impurities of not more than 0.2%, and total impurities of not more than 0.4%. Aurobindo complied with those requirements. A tablet with a trace impurity like [REDACTED] complied with USP specifications at that time.

80. [REDACTED]

[REDACTED]

81. **API Specifications and Test Methods.** The USP Valsartan Monograph (Official as of 01Jan2018) has tests for identification, assay, impurities, residue on ignition, and water content. The acceptance criteria for the assay are 98.0% to 102.0% on an anhydrous basis. The impurities acceptance criteria are not more than (NMT) 1.0% valsartan related compound A, NMT 0.2% valsartan related compound B, NMT 0.1% valsartan related compound C, NMT 0.1% any other individual impurity, and NMT 0.3% total impurities (excluding compound A). The assay and impurity assays are both based on HPLC with UV detection. The Aurobindo valsartan API met these USP criteria.

82. The Aurobindo DMF filed with the FDA [REDACTED]

[REDACTED]

[REDACTED] The Aurobindo valsartan API

met these criteria as well. Thus, the Aurobindo API met both USP and FDA requirements at the time.

83. **Recovered solvents.** The Memorandum states [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] (Plaintiffs' Memorandum of Law in Support of Their Motion for Class Certification of Consumer Economic Loss Claims at 37).

84. The use of recovered solvents is an accepted and customary practice, as noted in FDA's API Process Inspection Guidance. (FDA, Chapter 56 – Drug Quality Assurance, Active Pharmaceutical Ingredient (API) Process Inspection, <https://www.fda.gov/media/75201/download>). "Solvents can be recovered and reused in the same processes or in different processes provided that solvents meet appropriate standards before reuse or commingling." (*Id.* at 27).

85. The use of recovered solvents is also considered environmentally friendly. The alternative is to use virgin solvent, for which the generation and disposal of the solvent has a significant carbon footprint.

X. My Opinion Concerning the Expert Declaration of John L. Quick

86. **Labeling.** Mr. Quick states [REDACTED]
[REDACTED]
[REDACTED] (Expert Declaration of John L. Quick at 7).

87. [REDACTED]
[REDACTED]

88. The presence of potential impurities and degradation products in a drug product at this level is not required to be in the labeling given that the product met FDA approved specifications.

89. **SOPs.** Mr. Quick notes that the number one citation by FDA year after year is the following, "Procedures not in writing, fully followed". (Expert Declaration of John L. Quick at 11).

90. Adulteration is defined in the CFR. (21 U.S.C. § 351,

<https://www.govinfo.gov/app/details/USCODE-2011-title21/USCODE-2011-title21-chap9-subchapV-partA-sec351>). Some definitions of adulteration are fairly specific and obvious. For

example, the CFR states “If it consists in whole or in part of any filthy, putrid, or decomposed substance”. Other CFR definitions are general, such as “facilities or controls used for, its

manufacture, processing, packing, or holding do not conform to or are not operated or

administered in conformity with current good manufacturing practice”. (21 U.S.C. § 351(a)(1)).

This broad definition allows the FDA to cite hundreds of facilities each year, but not all citations indicate adulteration in each cited circumstance. Assessing adulteration requires assessment of the specific citation as applied to the specific facility and circumstances.

91. The citation of a facility for a cGMP concern does not necessarily indicate actual adulteration by the presence of a foreign or inferior substance or element. For example, [REDACTED]

92. **Risk management.** Mr. Quick cites FDA’s Guidance Q9 “Quality Risk Management”. (Expert Declaration of John L. Quick at 11). It should be noted that this guidance includes risk reduction and acceptance, acknowledging that one, risks cannot always be eliminated and two, risks may be acceptable given the risk-reward balance.

93. He also cites the FDA Guidance, “Control of Nitrosamine Impurities in Human Drugs”, but the initial version of this guidance was not issued until September 2020, long after the affected lots were manufactured. This guidance provides FDA’s published acceptable intake limits for nitrosamines. For NDMA and NDEA these limits are 96 and 26.5 ng/day based on 70 years of exposure. (Expert Declaration of John L. Quick at 11).

94. The unexpected detection of trace levels of NDEA in the valsartan API lots does not mean that Aurobindo had inappropriate quality risk management.

95. **Supplier Qualification.** Mr. Quick cites FDA's Contract Manufacturing Arrangements for Drugs:

Quality Agreements guidance. (Expert Declaration of John L. Quick at 13 n.21). This guidance notes that "Each party engaged in the manufacture of a drug is responsible for ensuring compliance with CGMP for the manufacturing activities it performs." (FDA, Contract Manufacturing Arrangements for Drugs: Quality Agreements, at 3, <https://www.fda.gov/media/86193/download>).

96. Aurobindo audited and qualified Lantech as a supplier. [REDACTED]

[REDACTED]

[REDACTED]

97. [REDACTED]

[REDACTED] and, as the FDA states, were "unexpected" (FDA, Control of Nitrosamine Impurities in Human Drugs, Guidance for Industry, at 1, <https://www.fda.gov/media/141720/download>). Thus, it is not reasonable to expect an audit to have discovered such an issue.

98. It can be difficult for a contracting company to be fully aware of every detail of a contract manufacturer's activities, despite audits and quality agreements. This is particularly true when it comes to trace impurities. [REDACTED]

[REDACTED]

99. **Recovered solvents.** Mr. Quick references FDA's API Process Inspection Guidance: "Solvents can be recovered and reused in the same processes or in different processes provided that solvents meet appropriate standards before reuse or commingling." (Expert Declaration of John L. Quick at 15).

100. As noted above, solvent recovery is a common and accepted manufacturing process, and in fact, is considered environmentally friendly.

101. Testing against a standard in no way means you would see a trace impurity unless you were specifically looking for it. This is true for a number of reasons including:

i) The assay or assays, most likely GC or HPLC, are most likely verifying one and/or two things

(1) Is the solvent the solvent of interest?

(2) Is there carry over of the primary compound from the previous use?

ii) Assays to verify the identity of the solvent are generally not designed to look for trace impurities, particularly for impurities that are not related to the solvent. For example, in the case of ethyl acetate, [REDACTED]

[REDACTED]

[REDACTED]

iii) The trace impurity may co-elute with another compound which is at a much higher concentration. Co-elution means that the two compounds come off the chromatography column and enter the detector at the same time.

iv) The trace impurity will likely not be eluted in these assays since the assay would not be designed to see it.

v) Even if it did elute, the trace impurity may be below the detection limit or the specification.

For example, in the case of ethyl acetate, [REDACTED]

[REDACTED]

The trace levels of NDEA being discussed here are orders of magnitude less than this [REDACTED]

[REDACTED]

102. While I was at USP on the Excipient Expert Committee, the issue of testing being unable to see unknown trace impurities was recognized and commonly discussed. When USP monographs were being updated, acceptance criteria were generally discussed to address

potential impurities so as to control them. It was considered impractical to test for unknown impurities, particularly at a trace level.

103. **Quality management.** Mr. Quick states [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED], and that [REDACTED]

[REDACTED]

[REDACTED] (Expert Declaration of John L. Quick at 20).

104. In my opinion, the above statement is not substantiated. Each firm is independent, with different quality systems, different scientists and managers, different facilities, different equipment, different data, different personnel, different vendors, and different processes and procedures.

105. Mr. Quick's statement is objectively inaccurate because [REDACTED]

[REDACTED]

Furthermore, the concentrations of NDMA and NDEA varied among manufacturers. Thus, each Manufacturer's products were not equally impacted.

106. **Risk assessments.** Mr. Quick states that Aurobindo had a [REDACTED]

[REDACTED] (Expert Declaration of John L. Quick at 34).

107. Aurobindo acted competently and appropriately [REDACTED]

[REDACTED] In fact, ICH M7, ASSESSMENT

AND CONTROL OF DNA REACTIVE (MUTAGENIC) IMPURITIES IN PHARMACEUTICALS TO LIMIT POTENTIAL CARCINOGENIC RISK, includes four options for controlling process related to impurities. Option 4 reads:

- i) “Understand process parameters and impact on residual impurity levels (including fate and purge knowledge) with sufficient confidence that the level of the impurity in the drug substance will be below the acceptable limit such that no analytical testing is recommended for this impurity.”
- ii) A Working Group in the International Consortium for Innovation and Quality in Pharmaceutical Development found that the industry follows ICH M7 Option 4 because it allows the utilization of process knowledge to reduce analytical testing without compromising patient safety. (Borths et al., Control of Mutagenic Impurities: Survey of Pharmaceutical Company Practices and a Proposed Framework for Industry Alignment, Org. Process Res. Dev., 2021, 25,4, 831–837).

108. Risk assessment using sound scientific principles is an established concept. The drug side of the FDA (CDER) formalized this in guidance issued in 2006 (Q9 Quality Risk Management). This guidance states that “the evaluation of the risk to quality should be based on scientific knowledge.” (FDA, C9 Quality Risk Management at 3, <https://www.fda.gov/media/71543/download>). The device side of the FDA (CDRH) formalized risk management in a 1997 guidance (DESIGN CONTROL GUIDANCE FOR MEDICAL DEVICE MANUFACTURERS). This guidance states that risk management “is intended to be a framework within which experience, insight, and judgment are applied to successfully manage risk.” (FDA, Design Control Guidance for Medical Device Manufacturers at 5, <https://www.fda.gov/media/116573/download>).

109. The FDA’s Nitrosamine Guidance lists possible causes of nitrosamine impurities:

- i) General Conditions That Lead to Nitrosamine Formation
 - (1) Formation of nitrosamines is possible in the presence of secondary, tertiary, or quaternary amines²² and nitrite salts²³ under acidic reaction conditions

ii) Sources of Secondary, Tertiary, and Quaternary Amines That Can Form Nitrosamines

(1) Amines may be present in a manufacturing process for a variety of reasons. The API (or API degradants), intermediates, or starting materials may contain secondary or tertiary amine functional groups. Tertiary and quaternary amines may also be added intentionally as reagents or catalysts.

(2) Amide solvents, which are susceptible to degradation under certain reaction conditions, are another source of secondary amines

iii) Contamination in Vendor-Sourced Raw Materials

iv) Recovered Solvents, Catalysts, and Reagents as Sources of Contamination

v) Quenching Process as a Source of Nitrosamine Contamination

(1) There is a risk of nitrosamine formation when a quenching step is performed directly in the main reaction mixture (i.e., when nitrous acid is added to the reaction mixture to decompose residual azide).

vi) Lack of Process Optimization and Control

(FDA, Control of Nitrosamine Impurities in Human Drugs, at 5–8, <https://www.fda.gov/media/141720/download>).

110. Items i, ii, v, and vi all involve the API synthesis. [REDACTED]

[REDACTED]

[REDACTED]

111. Items iii and iv involve residual “contamination,” and could result in trace levels of nitrosamines.

112. It should be noted that the authors of the Guidance had the advantage of prior knowledge when listing iii and iv, which is true for all of FDA’s nitrosamine findings.

113. Finally, Nitrosamines were not detected by multiple companies and the FDA on multiple drug products. I believe this was due at least in part to the extremely low levels of nitrosamines, the difficulty in detecting them, and their being unexpected.

114. In my opinion, Aurobindo's investigation was reasonable and in line with industry practice. Once the issue of nitrosamine impurities was known, Aurobindo identified the cause and took appropriate corrective actions which are described in detail above in paragraph 34.

XI. My Opinion of Statements in the Expert Declaration of Ron Najafi, Ph.D.

115. **RLD.** Dr. Najafi states "I have been retained by plaintiffs' counsel to provide an opinion on whether Valsartan which contains NDMA or NDEA is the same and/or chemical equivalent of the Reference Listed Products, Diovan and/or Exforge." (Expert Declaration of Ron Najafi, Ph.D. at 1).

116. He states that "The presence of the nitrosamine contamination found in the Valsartan products at issue here renders these products as not the same as the Reference Listed Drug, Diovan and/or Exforge." (*Id.*) He also states "Valsartan containing products that contained NDMA and NDEA were not the generic equivalent of Diovan or Exforge because they contained NDMA and NDEA." (*Id.* at 7).

- i) This is incorrect for the same reasons as stated above. He failed to identify any evidence showing that the API was not bioequivalent.
- ii) Furthermore, the FDA would not advise patients and health care professionals to continue using these products.

117. Dr. Najafi states "As a result, the Valsartan containing products with NDMA and NDEA were not the same as or chemically equivalent to the brand name Diovan or Exforge products because they contained NDMA and NDEA." (*Id.*).

- i) Dr. Najafi ignores that no two lots of the RLD are the same. They may reasonably vary in the levels of inactive and active ingredients, as well as in the levels of any impurities and degradation products.
- ii) Dr. Najafi uses the term “chemically equivalent,” (*id.* at 4) but this term is not in the Orange Book. The Orange Book does define Pharmaceutical Equivalents and Therapeutic Equivalents, and the Aurobindo products meet these definitions (which is why they are listed as AB). (FDA, Orange Book Preface, <https://www.fda.gov/drugs/development-approval-process-drugs/orange-book-preface>).

118. **“Sameness”**. Dr. Najafi states that “Generic drug manufacturers have an ongoing federal duty of sameness in their products.” (Expert Declaration of Ron Najafi, Ph.D. at 4).

- i) The CFR states that the generic will have the same active ingredient, same route of administration, same dosage form, and same strength. Aurobindo met those requirements.

119. He states that “A generic manufacturer (like a brand manufacturer) must also make “a full statement of the composition of such drug” to the FDA. (Expert Declaration of Ron Najafi, Ph.D. at 4). Additionally, in evaluating a drug product formulation and inactive ingredients, a generic manufacturer must compare its generic drug to the RLD’s formulation, not the formulation of the reference standard.”

- i) It is correct that the composition is disclosed in the ANDA.
- ii) It is incorrect that the generic drug must utilize the same inactive ingredients as the RLD.

(1) According to the FDA, “A generic drug may have certain minor differences from the brand-name product, such as different inactive ingredients. It is important to note that there will always be a slight, but not medically significant, level of expected variability—just as there is for one batch of brand-name medicine compared with the next batch of brand-name product. This variability can and does occur during manufacturing, for both

brand-name and generic medicines. When a medicine, generic or brand-name, is mass produced, very small variations in purity, size, strength, and other parameters are permitted.” (FDA, Generic Drugs: Questions & Answers,

<https://www.fda.gov/drugs/questions-answers/generic-drugs-questions-answers>).

iii) His reference to the formulation of the reference standard is unclear. The USP reference standard for valsartan is only composed of the API.

120. **Manufacturing changes.** Dr. Najafi states that “The FDA requires drug companies to continually assess all potential changes to their manufacturing processes because if these changes may result in, for instance, the formation of a new mutagenic or carcinogenic impurity in the product, it would impact whether the drug is the same as the RLD, in order to meet their duty of sameness.” (Expert Declaration of Ron Najafi, Ph.D. at 6).

121. Dr. Najafi appears to imply there was a post-approval change made to the API or drug product that was not disclosed to the FDA. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] I am not aware of any change to the drug product process that would result in a mutagenic or carcinogenic impurity.

122. Changes to an API process are discussed in the Change Control section of Q7, Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, which reads

- i) “The potential impact of the proposed change on the quality of the intermediate or API should be evaluated. A classification procedure may help in determining the level of testing, validation, and documentation needed to justify changes to a validated process. Changes can be classified (e.g., as minor or major) depending on the nature and extent of the changes, and the effects these changes may impart on the process. Scientific judgment should determine what additional testing and validation studies are appropriate to justify a change in a validated process.” (FDA, Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, Guidance for Industry, at 36, <https://www.fda.gov/media/71518/download>).

- ii) Note that there is no reference to the RLD. Scientific judgment is advised.

123. Dr. Najafi also refers to the FDA guidance entitled Changes to an Approved NDA or ANDA.

- i) Note that for drug product, “changes to equipment of the same design and operating principle” would be considered a minor change. (FDA, Guidance for Industry, Changes to an Approved NDA or ANDA, at 15, <https://www.fda.gov/media/71846/download>).

124. Postapproval changes are also discussed in FDA’s guidance Immediate Release Solid Oral Dosage Forms, Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation.

- i) A change as significant as a change in excipients amount, “expressed as percentage (w/w) of total formulation, less than or equal to” listed ranges would be a Level 1 change (“those that

are unlikely to have any detectable impact on formulation quality and performance”). (FDA, Immediate Release Solid Oral Dosage Forms, Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation at 6, <https://www.fda.gov/media/70949/download>). As stated above, I am unaware of postapproval changes in drug product.

125. Dr. Najafi also makes reference to M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals. (Expert Declaration of Ron Najafi, Ph.D. at 5 n.7, 6 n.8).

- i) M7 states “This guideline is not intended to be applied retrospectively (i.e., to products marketed prior to adoption of this guideline).” (FDA, M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk, at 6, <https://www.fda.gov/media/85885/download>) (underline added).
- ii) M7 also states “However, some types of post-approval changes warrant a reassessment of safety relative to mutagenic impurities.” (*Id.*)

(1) As noted above,

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] Thus, Dr. Najafi's implication that appropriate post-approval changes were not communicated with the FDA is unfounded.

(2) [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

126. **NDMA AND NDEA.** Dr. Najafi states that "NDMA and NDEA (nitrosamines) are not new, nor unexpected impurities. The existence of such compounds and their potential toxicity is well known since the 1970s. Further, the link between nitrate/nitrites and nitrosamine formation, as well as their effects on human health, have been discussed widely in the popular media for decades." (Expert Declaration of Ron Najafi, Ph.D. at 6).

- i) Dr. Najafi's statement is in clear contradiction with the FDA's position and the industry's experience manufacturing VCDs. The preface to the FDA's Nitrosamine guidance (issued Feb 2021) states "FDA is implementing this guidance without prior public comment ... FDA made this determination because of the importance of providing timely information to manufacturers regarding risk assessments, testing, and other appropriate actions they should take to reduce and mitigate nitrosamine impurities in active pharmaceutical ingredients (APIs) and drug products." (FDA, Control of Nitrosamine Impurities in Human Drugs, Preface, <https://www.fda.gov/media/141720/download>). The Introduction goes on to say "The recent unexpected finding of nitrosamine impurities, which are probable human carcinogens, in drugs such as angiotensin II receptor blockers (ARBs), ranitidine, nizatidine, and metformin, has made clear the need for a risk assessment strategy for potential nitrosamines in any pharmaceutical product at risk for their presence." (*Id.* at 1) (emphasis added).

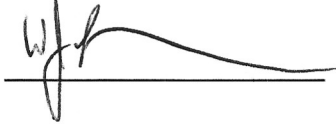
- ii) Issuing a guidance without a public comment period is rare and is generally withheld for unique circumstances.
- iii) The FDA's statement is clearly at odds with Dr. Najafi's opinion that this issue has been known for decades and that it was to be expected.
- iv) I also searched the FDA's database which lists recalls (<https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts>). There are 40, 14, and 9 recalls related to NDMA, NDEA, and nitrosamines, respectively. These recalls began on July 16, 2018 and continued into 2021. The FDA and many companies were surprised by the nitrosamine findings.

XII. Conclusions

127. The FDA issues hundreds of Form 483s and Warning Letters, each with one or more observations, every year due to perceived non-compliance with cGMPs. Not all observations are valid. An observation on a Form 483 does not constitute a final agency determination that any condition is in violation of federal law.
128. The Aurobindo VCDs met the applicable FDA and USP standards at the time, were approved AB generics listed in the Orange Book, and were bioequivalent to the respective RLDs.
129. The FDA advised that patients taking prescription medications with potential nitrosamine impurities should not stop taking their medications.
130. The FDA has published regulatory guidance setting acceptable intake levels for nitrosamines in medications.
131. The FDA's acceptable intake levels for nitrosamines are so low that sensitive analytical procedures are required to detect them.
132. [REDACTED]
- [REDACTED]

133. All drug products, including the RLDs, vary from lot to lot in regard to the presence of impurities, as well as the levels of API and inactive components.
134. The use of non-dedicated equipment is common in the industry and is allowed by the FDA.
135. Equipment cleaning in the industry focuses on the active ingredient.
136. Reduced testing of raw materials once a vendor is qualified is an acceptable and recognized industry practice and is allowed by the FDA.
137. The use of recovered solvents is customary in the industry, is allowed by the FDA, and is environmentally friendly.

Dated: January 12, 2022

A handwritten signature in black ink, appearing to be 'WJ Lambert', is written over a horizontal line.

William J. Lambert, Ph.D.

Appendix A

Materials Considered
PageID: 69436

Complaints	
Plaintiffs' Consolidated Third Amended Master Economic Loss Class Action Complaint (Valsartan)	
Plaintiffs' Consolidated Third Amended Master Medical Monitoring Class Action Complaint (Valsartan)	
Plaintiffs' Second Amended Master Personal Injury Complaint (Valsartan)	
Deposition Transcripts	
3/19/2021 Deposition of Bhadresh Doshi and Attached Exhibits	
4/15/2021 Deposition of Blessy Johns and Attached Exhibits	
5/27/2021 Deposition of David Palew and Attached Exhibits	
4/30/2021 Deposition of Dr. Ambati Rama Mohana Rao and Attached Exhibits	
3/25/2021 Deposition of Harsha Vardhana Prasad Gorijavolu and Attached Exhibits	
4/16/2021 Deposition of Jasleen Gupta and Attached Exhibits	
4/28/2021 Deposition of Sandra Martinez and Attached Exhibits	
5/20/2021 Deposition of Sanjay Singh and Attached Exhibits	
5/21/2021 Deposition of Sanjay Singh and Attached Exhibits	
5/18/2021 Deposition of Steve Lucas and Attached Exhibits	
Motions & Briefs	
Third Party Payors' Brief in Support of Motion to Certify Class and Attached Exhibits	
Medical Monitoring Plaintiffs' Memorandum of Law in Support of Motion for Class Certification and Attached Exhibits	
Plaintiffs' Motion for Class Certification of Consumer, Third Party Payor and Medical Monitoring Claims and Attached Exhibits	
Plaintiffs' Memorandum of Law in Support of Their Motion for Class Certification of Consumer Economic Loss Claims and Attached Exhibits	
ANDAs	
The ANDA for Valsartan Tablets (202223) including filings 0000 through and including 0051 including filings 0000 through and including 0033, Acceptance Letter - 27-09-2010, Final approval letter - 2015-Jan-05, and Tentative Approval Letter - 2013-Apr-19	
The ANDA for Amlodipine & Valsartan Tablets USP (206512) including filings 0000 through and including 0033, Acceptance Letter - 2014-May-28, and Approval letter - 22-Apr-2016	
The ANDA for Valsartan & Hydrochlorothiazide Tablets USP (202519) including filings 0000 through and including 0036, Acceptance Letter - 16-Feb-2011, and Approval letter - 21-Mar-2013	
FDA Guidance Documents (https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs)	
Q1E	
Q3A	
Q3B	
Q3C and Appendices	
Q3C — Tables and List	
Q3D	
Q7	
Q7 Q&A	
Q7A	
Q8	
Q9	
Q10	
Q 8-10 Q&A	
M7 and Addendum	
M7 Q&A	

M9
Control of Nitrosamine Impurities in Human Drugs
Immediate Release Solid Oral Dosage Forms, Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation
Postapproval Changes to Drug Substances
FDA Website Pages
Guideline for Submitting Documentation for the Manufacture of and Controls for Drug Products
APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS ("Orange Book"); https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm
DESIGN CONTROL GUIDANCE FOR MEDICAL DEVICE MANUFACTURERS
Recalls, Withdrawals, and Safety Alerts Page; https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts
Information About Nitrosamine Impurities in Medication; https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications
Facts About Current Good Manufacturing Practices (CGMPs); https://www.fda.gov/drugs/pharmaceutical-quality-resources/facts-about-current-good-manufacturing-practices-cgmps
Inspections, Compliance Enforcement and Criminal Investigations; https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/inspection-observations
FDA Form 483 Frequently Asked Questions; https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/fda-form-483-frequently-asked-questions
Federal Food Drug and Cosmetic Act (FD&C Act); https://www.fda.gov/regulatory-information/laws-enforced-fda/federal-food-drug-and-cosmetic-act-fdc-act
Drugs@FDA Glossary of Terms; https://www.fda.gov/drugs/drug-approvals-and-databases/drugsfda-glossary-terms#R
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Auro-MDL 2875-0020761
Auro-MDL 2875-0077806
Auro-MDL 2875-0077957
Auro-MDL 2875-0078124

Start Bates Number
Auro-MDL 2875-0079232
Auro-MDL 2875-0079264
Auro-MDL 2875-0080223
Auro-MDL 2875-0086386
Auro-MDL 2875-0086387
Auro-MDL 2875-0092698
Auro-MDL 2875-0104586
Auro-MDL 2875-0113540
Auro-MDL 2875-0113985
Auro-MDL 2875-0604253

Appendix B

CURRICULUM VITAE

NAME: William J. Lambert, Ph.D. (Bill)

CONTACT INFORMATION:

pharmsci.BL@gmail.com
1-206-678-5949
PO Box 3032
Incline Village, NV 89450

SUMMARY:

- Bill's 30+ years of experience includes:
- Executive team membership reporting to CEO for two public companies including one that was venture capital funded and had a successful product launch and IPO
- Writing and review of Module 3 CMC section of eCTD regulatory filings (IND, IMPD, NDA)
- Experience working with corporate board of directors
- Significant experience in due diligence and consulting business development groups from both the acquirer and acquiree standpoint
- Member of multiple development leadership teams for both big pharmaceutical and big biotech companies
- Optimization and lead selection of drug candidates, both large and small molecule
- Experience managing CMOs, CDOs, and CROs
- Contributed to the development and global regulatory registration efforts of several marketed drugs including Corvert (anti-arrhythmic), Trovan (antibiotic), Halaven (anti-cancer), Exparel (post-surgical pain), Fasenra (benralizumab, asthma), and Omidria (ophthalmic surgery)
- Experience in discovery support, development, sourcing, and commercial operations.
- Managed budgets of up to \$20MM
- Knowledgeable in intellectual property including the management of a large patent portfolio
- Member of multiple scientific advisory boards
- Subject matter expert in sterile product formulation and analytical development, aseptic processing, tech transfer, drug delivery, device-drug combination products, cGMPs, and life cycle management

EXPERIENCE:**Module 3 Pharmaceutical Consulting**, Reno, NV, April 2018 - present

Pharmaceutical Development, CMC, and Drug Delivery Consultant

Provides expert consultation in the following areas:

- CMC sections of eCTD regulatory filings (IND, IMPD, NDA, BLA)
- Due diligence assessments of pharmaceutical products, manufacturing facilities, drug delivery technologies, and regulatory filings
- Optimization and lead selection of drug candidates, both large and small molecule
- Expert witness and/or advice on drug formulation, intellectual property, and manufacturing-related litigation cases
- Sterile product development, lyophilization (freeze drying), injectable sustained release, device-drug combination products, and aseptic processing
- Life cycle management

Omeros Corporation, Seattle, WA, Jan. 2015-Apr. 2018

Vice President, Chemistry, Manufacturing, and Controls, reporting to Chairman / CEO

- Responsible for all CMC aspects of the Company's drug substances and drug products from development through and including manufacturing.
- Lead formulation, process, and analytical development, manufacturing, logistics and supply chain management, and quality control for both biological and chemical drug substances and products.
- Oversee all CMC-related regulatory reports and submissions.
- Ensure compliance with all applicable regulatory guidelines.
- Negotiate third-party contracts including commercial supply agreements

MedImmune/AstraZeneca, Gaithersburg, MD, Oct. 2011-Jan. 2015

Fellow and Head, Innovative Drug Delivery Group (Director level)

- The Innovative Drug Delivery Group is charged with identifying, assessing and developing drug delivery technologies for use with MedImmune protein and peptide drugs and vaccines. These technologies include formulation- and device-based technologies. Projects include novel devices for late-stage candidates as well as the application of enabling technologies in collaboration with Research (e.g., sustained release technologies, alternative routes of administration).
- Led team evaluating wearable subcutaneous large volume injectors and negotiation of a development agreement.
- Combination product device experience includes accessorized prefilled syringes, autoinjectors, pens, and wearable large volume bolus injectors. Experienced in reviewing and approving design controls (design history file, user requirements specifications, design verification and validation, and product specifications), human factors engineering studies, and risk management plans (design, user, and process failure mode, effects and criticality analyses (FMECA)).
- Co-chair of the Novel Drug Delivery Network which coordinates delivery efforts and needs assessments with colleagues in the AstraZeneca group.
- Multiple due diligence assignments including lead of CMC teams.

- Member of the Development Leadership Team, Technology Research Review Committee, Biosuperiors Innovative Medicine Steering Committee, the Science and Collaboration Committee, and regulatory filing review teams. Previous activities included the Contract Acceleration Committee, Biopharmaceutical Development Promotion Committee, and the Formulation Sciences Review Committee.

UCSD Extension, San Diego, CA (2010-present)

Instructor teaching course Dosage Form Design and Development

Pacira Pharmaceuticals, Inc. (formerly SkyePharma, Inc.), San Diego, CA,

Jan. 2006-Sept. 2011

Sr. Vice President, Pharmaceutical Development, part of the Executive Team, reporting to CEO / President

- Demonstrated leadership of customer-oriented teams developing traditional and protein therapeutics in the areas of formulation, analytical, clinical supply manufacture, scale-up, tech transfer, CMC and preclinical regulatory filings, and manufacturing technical support.
- Successfully filed the CMC and preclinical sections of an IND and IMPD for initiation of the company's lead internal Phase 2/3 program (no CMC questions were received). Successfully scaled up a complex formulation process for the above product, developed and validated all analytical assays for the NDA 505(b)(2) stability program, initiated all necessary preclinical tox and PK programs, and transferred the product to Operations (product approved: Exparel®).
- Responsible for identification and enablement of new product ideas including the company's two lead pipeline projects
- Spearhead feasibility testing utilizing the company's DepoFoam® multivesicular liposome technology to partner company compounds (e.g., Amylin, Novo Nordisk). Co-led technical and negotiation discussions with business development leading to development and licensing agreements with values over \$10MM in achieved milestone payments and total deal values of nine-figures in milestones and royalties.
- Led device injectability efforts of the DepoFoam technology leading to a patent application for use with hyaluronidase and a novel approach for assessing viscosity in narrow gauge needles.
- Initiated analytical and process improvements which have dramatically impacted yield, reproducibility, scalability, and process understanding. One project progressed from the 10 mL to 3L scale (including making tox and cGMP Phase 1 supplies) in just 6 months (a 3 to 4-fold improvement in timing from the old process).
- Experienced with business development and due diligence activities, including those with venture capital groups, partner licensing, and a successful initial public offering.
- Led technical writing of three Patient Protection and Affordable Care Act (PPACA) grants totaling \$513,000.
- Manage the intellectual property portfolio for the company (over 14 patent families)
 - Initiated new strategy in order to focus on critical applications and territories leading to six-figure annual savings

- Selected new outside counsel leading to improved filing strategies and successful European grant providing composition of matter claims for key product for several years beyond existing patent coverage
- Responsible for several new patent applications supporting company pipeline and partner projects
- Successfully oversaw IP due diligence during initial public offering and multiple partner agreements

Eisai Inc., Research Triangle Park, NC (1997-2006)

Senior Director of Drug Delivery Technology, Pharmaceutical and Analytical R&D, April 2004-Jan. 2006 reporting to VP of PAR&D

- Identified life cycle management opportunities by leveraging drug delivery and formulation enabling technologies, and led the internal/external teams. Projects included oral controlled release, rapid dissolving, topical, and injectable products.
- Member of the corporate “Pipeline” Committee which evaluated licensing opportunities
- One project I identified received the highest net present value of any worldwide R&D project; in-house and outside oral pulsatile delivery technology projects were started, and an NDA was filed.

Director of Product Development, Pharmaceutical and Analytical R&D, July 1997- March 2004 reporting to VP of PAR&D

- Managed day to day operations and provided overall scientific leadership for a group responsible for formulation development of drug candidates from US, UK, and Japanese discovery groups through commercialization (including technical transfer to a commercial facility). Led the filing of several IND drug product CMC sections.
- This group won two global scientific achievement awards and brought two key projects sepsis and cancer areas (the later marketed as Halaven[®]) to Phase 3 studies.
- Led application of Kepner Tregoe problem solving analysis within company to identify the root cause of various formulation and process challenges that arose. One unusual stability challenge was rapidly and successfully addressed on a critical project without any impact on project timelines.
- Responsible for start-up, maintenance, validation, and scheduling of a GMP manufacturing facility which is the sole supplier of non-cytotoxic injectable clinical supplies world-wide for Eisai (had a freeze drying and terminal sterilization capability). This facility was functional and underwent a successful FDA inspection within only two years of construction.
- Provided technical support for US regulatory filings and an affiliated commercial tablet facility
- Member of the “Leadership 55” Committee which provided guidance and direction to the company

Pfizer Central Research, Groton, CT, April 1991-July 1997

Pharmaceutical R&D, Liquids Development, Sr. Research Investigator (promoted from Sr. Research Scientist)

- Managed a group responsible for physical-chemical characterization, development, and scale-up of parenteral and enteral liquid formulations of traditional and protein drugs (discovery through marketing)
- Represented Developmental R&D (Pharmaceutical, Analytical, Process, and Bioprocess R&D) at the Project Team level for various therapeutic classes of human and animal health drugs
- Lead formulation scientist on an IV sterile product (SVP and LVP) development program which led to a marketed antibiotic product (Trovan[®])
- Other projects included sustained release parenteral formulations and device-based delivery of peptides, market research for IV packaging, oral suspension development and manufacture, and freeze drying optimization

The Upjohn Company, Kalamazoo, MI (1987-1991)

Research Scientist, Drug Delivery R&D-Pharmaceutics/Biotechnology, June 1990-April 1991

- Formulation development and manufacture for protein and peptide drugs/vaccines

Research Scientist, Drug Delivery R&D-Sterile Products, March 1988-May 1990

- Formulation development and scale-up for parenteral dosage forms.
- Formulation scientist on the first Upjohn team to bring a candidate to Phase 1 in under one year (Corvert[®], anti-arrhythmic).

Scientist, Pharmacy Research, Jan. 1987-Feb. 1988

- Preformulation investigation and formulation development through early clinical trials

The above positions included responsibility for representation of the Unit for the Project Team, drug candidate and technology assessment, and the supervision of BS/MS level associates.

Maple Village Pharmacy, Ann Arbor, MI, Pharmacist/Manager, Oct. 1981-July 1982.

The Upjohn Company, Kalamazoo, MI, Pharmacy Research, Summer Scholar, 1981. Studied the mechanism of hydrolysis of methylprednisolone prodrugs under B.D. Anderson.

Lederle Laboratories, Pearl River, NY, National Pharm. Council Intern, May-August 1980.

EDUCATION:

University of Utah, Ph.D., Pharmaceutics; GPA 3.88; Under Distinguished Professor W.I. Higuchi. Thesis: Mechanistic Study of Stratum Corneum Barrier Function; Included collaborative studies with N.B. Graham, U. Strathclyde, P. Banerjee, SmithKline Consumer Products, and W.Z. Plachy, San Francisco State U.

University of Michigan, Pharmaceutical Chemistry; under W.I. Higuchi; GPA 8.3/9

University of Rhode Island, B.S., Pharmacy; GPA 3.64

Undergraduate Research Project: Effects of Humidity on Tablet Matrices, Prof. J. Lausier.

HONORS:

Invited Guest Editor for AAPS PharmSciTech themed issue (2010)

Quoted in PharmaVoice article titled Delivering New Hope, Jan 2008

‘Top Reviewer’ for J Pharm Sci, 2008, 2020.

2003 and 2004 Eisai PAR&D Technical Achievement Award

2002 Eisai PAR&D Team Player Award

2001 Eisai Corporate Award for Scientific Achievement

1982-85 AFPE J.K. Lilly Memorial Fellowship

University of Utah Graduate Research Fellowship

Phi Kappa Phi National Honor Society and National Dean's List

Rho Chi Pharmacy and U.R.I. Greek Honor Societies

ACTIVITIES:

Lecturer in the University of Maryland’s course titled Drug and Biologic Development (2014-present)

Lecturer in the Drug and Device Development course at the Uniformed Services University of the Health Sciences, Bethesda, MD (2013)

Grant Board for the American Association of Pharmaceutical Scientists (2014-2016)

Grant Board for the American Foundation for Pharmaceutical Education (2013-2014)

NIH Peer Reviewer, 2012, 2014

Controlled Release Society Annual Meeting Program Committee for 2015

Editorial Advisory Board of the Journal of Pharmaceutical Sciences (1994-present)

Advisory Board for the Handbook of Pharmaceutical Excipients (2002-present)

Boulder Peptide Society Scientific Advisory Board (2014-2015)

Sci and Ed Advisory Council for the National Inst. for Pharm. Tech and Ed (2006-present)

USP Council of Experts Excipient Committee Member, 2010-2015

NC Pharmaceutical Discussion Group, President (2003) and Program Chair (2002)

Leadership for Technical Managers, Center for Creative Leadership, Greensboro, NC (1995)

Kellogg School of Management Executive Course on Strategic Marketing for the Healthcare Industry (2004)

Pharmaceutical Manufacturers Association/AAPS Visiting Scientist (1988-1997)

Amer. Assoc. of Pharm. Scientists: Biotech, PDD, PT and Arden House Program Committees (1998 chair), PT Section Chair (2006), Member At Large- Publications Board (2001-2004)

American Chemical Society, Parenteral Drug Association, Int. Society of Pharm. Eng., Licensing Executives Society

CITIZENSHIP: USA and Ireland

PUBLICATIONS:

“Featured Article”, Strickley, R.G. and Lambert, W.J., A Review of Formulations of Commercially Available Antibodies, *J Pharm Sci*, 110(7), 2590-2608, 2021, <https://doi.org/10.1016/j.xphs.2021.03.017>.

Lambert, W.J., Due Diligence Assessment of CMC Activities, *Pharm Tech Reg Sourcebook*, Oct 2020, <https://www.e-digitaleditions.com/i/1302985-pharmtech-regulatory-sourcebook-october>.

Lambert, W.J., Commentary: Why do the majority of submissions for bridging from a prefilled syringe to an autoinjector include bioequivalence studies in order to demonstrate comparability? *AAPS J.*, 22:72, 2020, DOI: 10.1208/s12248-020-00453-0.

Lambert, W.J., The Selection of Excipients for Injectable Formulations, *Handbook of Pharmaceutical Excipients*, 9th Ed., Pharmaceutical Press, 2020.

Doughty, D.V., Clawson, C.Z., Lambert, W.J., and Subramony, J.A., Understanding Subcutaneous Tissue Pressure for Engineering Injection Devices for Large-Volume Protein Delivery, *J Pharm Sci*, 105(7), 2105-13, 2016.

Lambert, W.J., Considerations in Developing a Target Product Profile for Parenteral Pharmaceutical Products, *AAPS PharmsSciTech*, 11(3), 1476-1481, 2010.

Lambert, W.J. and Los, K., DepoFoam[®] Multivesicular Liposomes for Sustained Release of Macromolecules in Modified-Release Drug Delivery Technology, Vol 2, 2nd ed, Rathbone, Hadgraft, Roberts, and Lane-eds., Informa Healthcare, NY, NY, 2008, pp. 207-214.

Lambert, W.J., Drug Delivery: What the Future Holds, *BioPharm International*, 32-39, August 2007.

Lambert, W., Richard, B., Schrier, J., and Ying, P. Phospholipid monograph and Lambert, W., Petrolatum and Lysine HCl monographs, in *Handbook of Pharmaceutical Excipients*, Pharmaceutical Press (various dates from 2006-present).

Wang, Z., Burrell, L.S., Lambert, W.J., Solubility of E2050 at Various pH: A Case in Which Apparent Solubility is Affected by the Amount of Excess Solid, *J. Pharm. Sci.*, 91, 1445-1455 (2002).

Wang, Z., Frankel, B.A., Lambert, W.J., Determination of Moisture in Rubber Stoppers: Effect of Karl Fischer Oven Temperatures, *PDA J. Pharm. Sci. Tech.*, 55, 162-170 (2001).

Burrell, L.S., Carver, M.W., DeMuth, G.E., Lambert, W.J., Development of a Dye Ingress Method to Assess Container-Closure Integrity: Correlation to Microbial Ingress, *PDA J. Pharm. Sci. Tech.*, 54, 449-455 (2000).

Abraham, M.H. et al., Determination of solute lipophilicity as logP(octanol) and logP(alkane) using poly(styrene-divinylbenzene) and IAM stationary phases in RP-HPLC, *J. Chromatogr. A*, 766, 35-47 (1997).

Lambert, W.J.; Stamper, G.F. Development of an Analytical Reversed-Phase HPLC Assay for Transforming Growth Factor-beta 3, *J. Chromatogr. A*, 709 (2) 249-256 (1995).

Stamper, G.F.; Lambert, W.J. Accelerated Stability Testing of Proteins and Peptides: pH-Stability Profile of Insulinotropin Using Traditional Arrhenius and Non-linear Fitting Analysis, *Drug Devel. Indust. Pharm.*, 21, 1503-1511 (1995).

Lambert, W.J.; Peck, K.D. Development of an In Situ Forming Biodegradable Poly-lactide-co-glycolide System for the Controlled Release of Proteins, *J. Controlled Release*, 33, 189-195 (1995).

Brophy, R.T.; Lambert, W.J. The Adsorption of Insulinotropin to Polymeric Sterilizing Filters, *J. Parenteral Sci. Tech.*, 48, 92-94 (1994).

Lambert, W.J. Modeling Oil/Water Partitioning and Membrane Permeation using Reverse-Phase Chromatography, *J. Chromatogr.*, 656, 469-484 (1993) Invited review.

Lambert, W.J.; Kudla, R.J.; Holland, J.M.; Curry, J.T. A Biodegradable Transdermal Penetration Enhancer based on N-(2-hydroxyethyl)-2-pyrrolidone I. Synthesis and Characterization, *Int. J. Pharm.*, 95, 181-192 (1993).

Osborne, D.W.; Lambert, W.J. Computational Method of Predicting Optimization of Prodrugs or Analogues Designed for Percutaneous Delivery, in *Prodrugs: Topical and Ocular Drug Delivery*; Sloan, K.B., ed., Marcel Dekker, 1992.

Lambert, W.J.; Timmer, P.G.; Walters, R.R.; Hsu, C.L. Racemization and Intramolecular Nucleophilic Substitution Reactions of Ibutilide, *J. Pharm. Sci.*, 81, 1028-1031 (1992).

Lambert, W.J.; Timmer, P.G. Racemization of Ibutilide in Solution: A Factor to Consider when Choosing to Develop the Racemate or a Single Enantiomer, *Pharm. Res.*, 8, 1444-1447, (1991).

Lambert, W.J.; Middleton, D.L. pH Hysteresis Effect with Silica Capillaries in Capillary Zone Electrophoresis. *Anal. Chem.*, 62, 1585-7 (1990).

Lambert, W. J.; Wright, L. A.; Stevens, J. K. Development of a Preformulation Lipophilicity Screen Utilizing a C-18 Derivatized Polystyrene-Divinylbenzene HPLC Column. *Pharm. Res.*, 7(6) 577-586 (1990).

Lambert, W. J.; Dalga, R. J. Potentiometric Determination of Thermodynamic and Apparent Dissociation Constants by Nonlinear Least Squares Fitting. *Drug Devel. Ind. Pharm.*, 16(4) 719-737 (1990).

Lambert, W. J. BUFCALC: A Program for the Calculation of Buffers of Specified pH, Ionic Strength, and Buffer Capacity. *J. Chem. Ed.*, 67(2) 150-153 (1990).

Dalga, R. J.; Lambert, W. J. Development of a Polymer-Based Stability Indicating Assay for U-78,608, an Iron Complexing Monocarbam Antibiotic. *J. Chromatogr.*, 477(2), 427-433 (1989).

Lambert, W. J.; Higuchi, W. I.; Knutson, K.; Krill, S. L. Dose Dependent Enhancement Effects of AZONE on Skin Permeability. *Pharm. Res.*, 6(9), 798-803 (1989).

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Lambert, W. J.; Wright L. A. Prediction of Alkane/Water Partition Coefficients using a C-18 Derivatized Polystyrene-Divinylbenzene Stationary Phase. *J. Chromatogr.*, 464, 400-404 (1989).

Knuston, K.; Krill, S. L.; Lambert, W. J.; Higuchi, W. I. Physicochemical Aspects of Transdermal Permeation, *J. Controlled Release*, 6, 59-74 (1987).

Knuston, K.; Krill, S. L.; Lambert, W. J.; Higuchi, W. I. Probing the Stratum Corneum on the Molecular Level. In *Controlled Release Technology, Pharmaceutical Applications*; Lee, P. I.; Good, W. R., Eds., American Chemical Society, 1987.

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Baker, D. C.; Kumar, S. D.; Waites, J.; Arnett, G.; Shannon, W. M.; Higuchi, W. I.; Lambert, W. J. Synthesis and Evaluation of a Series of 2'-O-Acyl Derivatives of Ara-A as Antiherpes Agents. *J. Med. Chem.*, 27, 270 (1984).

ISSUED PATENTS:

Garcia, L.D., Zhu, L., Lambert, W.J., Patou, G.; Sustained release formulation of a non-steroidal anti-inflammatory drug, United States Patent 9,974,744 and 10,123,974.

Garcia, L.D., Gibson, L., Lambert, W.J., Li, B.W., Zhu, L., Sustained release formulation of methotrexate as a disease-modifying antirheumatic drug (DMARD) and an anti-cancer agent, United States Patent 9,770,414 and 10,028,911

Lambert, W. and Wang, Z., System and Method for Measuring Freeze Dried Cake Resistance, United States Patent 6,643,950.

Yesook, K., Lambert, W.J., Qi, H., Gelfand, R.A., Geoghegan, K.F., Danley, D.E, Prolonged delivery of peptides, United States Patents 6,828,303 and 6,284,727.

SELECTED PRESENTATIONS:

Lambert, W.J., Challenges with High Concentration Protein Solutions: Viscosity, Delivery of Large Volumes, and Device Considerations, Controlled Release Society Annual Meeting, Seattle, WA, 2016 (invited).

Lambert, W.J., Formulation and delivery considerations for subcutaneous administration, 5th Drug Formulation, Solubility, and Bioavailability Conference, Philadelphia, 2016.

Lambert, W.J., Approaches for Subcutaneous Delivery of Volumes Greater than 1 mL, Informa 2nd Annual Pre-Filled Syringes & Novel Injector Devices, Berlin, Germany, 2013 (invited keynote).

Lambert, W.J., The Role of Drug Delivery and Device Technologies for Peptide Products, TIDES Oligonucleotide and Peptide Technology and Product Development Conference, Boston, MA 2013 (invited keynote).

Lambert, W.J., Technical Challenges to Consider for Biologic Products and Injection Devices PepTalk, Palm Springs, CA, 2013.

Lambert, W.J., The Next Generation of Biologics and the Role of Drug Delivery and Device Technologies, BioProcess International Conference, Providence, RI, 2012 (invited keynote).

Lambert, W.J., A Current Market Overview of the Injectable Technology Landscape, World Pre-filled Syringe Summit, Washington, DC 2012 (invited chair).

Onel, E., Warnott, K., Markvicka, T., Lambert, W., and Patou, G., Pharmacokinetics of depobupivacaine (Exparel), a novel bupivacaine extended-release liposomal injection, in volunteers with moderate hepatic impairment. Clinical Pharmacology & Therapeutics, 2011.

Lambert, W.J., Controlled Release and Targeted Liposomal Drug Delivery Systems for Biotherapeutics, 2011 Arden Conference, West Point, NY and Seoul, Korea (invited).

Lambert, W.J., Injection Devices for Controlled Release Systems, Pep Talk 2011, San Diego, CA, (invited).

Lambert, W.J., The use of liposomes to provide sustained and targeted delivery of peptides, Peptide Formulation and Product Development Forum, Vienna, Dec 2010 (invited).

Lambert, W.J., Sustained Delivery of Proteins and Peptides: Experience with Multivesicular Liposomes, PepCon 2010, Beijing, China, (invited).

Lambert, W.J., Drug Delivery Technologies and Product Life-Cycle Management, Pep Talk 2010, San Diego, CA, (invited).

Lambert, W.J., Multivesicular Liposomes for the Sustained Delivery of Proteins and Peptides, 14th International Symposium on Recent Advances in Drug Delivery Systems, Feb., 2009, Salt Lake City, UT (invited).

Lambert, W.J., The 2008 Technology Landscape, Drug Delivery Partnerships, Jan. 2008, San Diego, CA.

Lambert, W.J., DepoFoam Multivesicular Liposomes for the Sustained Systemic Delivery of Proteins, ACS Western Regional Meeting, Oct. 2007 (invited).

Lambert, W.J., Ophthalmic Drug Delivery using DepoFoam Multivesicular Liposomes, Ophthalmic Drug Development and Delivery Summit, Sept. 2007, San Diego, CA.

Lambert, W.J., Sterile Products 101, AAPS 2006, San Antonio, TX.

Lambert, W.J., 1998 Arden House Conference Faculty, "Current Issues in Parenteral Product Development: Formulation Design, Packaging, Processing, and Regulation"

Lambert, W.J., Excipient Compatibility Considerations for Injectable Formulations, AAPS, 1996, Seattle, WA (invited symposium).

Lambert, W.J.; Grucza, R.A.; Stamper, G.F.; Chrnyk, B., Self-association and Concerted Conformational Changes of Insulinotropin, AAPS, 1994, San Diego, CA.

Lambert, W.J. An Introduction to Freeze Drying, AAPS Symposium on Freeze Drying of Pharmaceuticals: Advances in Process Control and the Formulation of Labile Materials, 1993, Orlando, FL.

Lambert, W.J. An Introduction to Capillary Electrophoresis. AAPS Symposium on Capillary Electrophoresis for the Analysis of Pharmaceuticals, 1990, Las Vegas.

Kissinger, L.D.; Lambert, W.J.; Tengwell, J.A.; Anderson, M.J.; Timmer, P.G. Terminal Sterilization Feasibility of a Bacteriocidal Injectable Solution of the Investigational Antiarrhythmic Agent U-70226E. AAPS, 1990, Las Vegas.

Lambert, W. J. Oil-Water Partition Coefficients: Estimation by Reversed-Phase HPLC Capacity Factor. ACS Symposium on Colloid Science and Solution Chemistry in Separation Science, 1990, Boston, MA (invited).

Lambert, W. J.; Wright, L. A.; Stevens, J. S. Development of a Preformulation Lipophilicity Screen Utilizing the Act-I HPLC Column. I. Test for Specific Solute-Stationary Phase Interactions, II. Thermodynamic and Extrathermodynamic Studies of Retention. AAPS, 1989, Atlanta, GA.

Lambert, W. J.; Brickner, S. J.; Douglas, S. L.; Morozowich, W.; Barsuhn, C. L.; Bronson, G. E. Preformulation Characterization of an N-Acyl Azetidinone Antibiotic (U-70,585) in a Rat Intestinal Absorption Model. AAPS, 1988, Orlando, FL.

Lambert, W. J.; Knutson, K.; Krill, S. L.; Higuchi, W. I. Mechanistic Studies of Stratum Corneum Permeability: I. Effects of Temperature on The Lipid Pathway, II. Molecular Level Studies, III. Effects of Long Term Hydration Leading to the Development of Aqueous Channels. APhA Academy of Pharmaceutical Sciences, 1985, Minneapolis, MN.

Lambert, W. J.; Knutson, K.; Banerjee, P.; Higuchi, W. I. Effect of Temperature on Permeability of Hydrocortisone Through Hairless Mouse Skin. APhA Academy of Pharmaceutical Sciences, 1984, Philadelphia, PA.

Mahjour, M.; Kusai, A., Lambert, W. J.; Ho, N. F. H.; Fox, J. L.; Higuchi, W. I. Enhancement of Topical Drug Delivery via Ester Prodrug Mixtures I. Solubilities, Esterase Activities, and Andenosine Deaminase Activities in Mixtures of 5'-O- Monoesters of Ara-A. APhA Academy of Pharmaceutical Sciences, 1982, San Diego, CA.

**UNITED STATES DISTRICT COURT
DISTRICT COURT OF NEW JERSEY**

IN RE: VALSARTAN PRODUCTS LIABILITY
LITIGATION

Case No. 1:19-MD-2875-rbk

Supplement and Amendment to the Expert Report of William J. Lambert, Ph.D.

March 4, 2022

RESTRICTED CONFIDENTIAL

SUBJECT TO PROTECTIVE ORDER

REDACTED

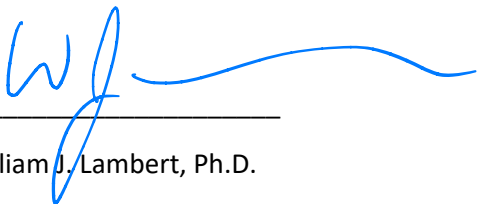
Supplement to Appendix A, Materials Considered

Start Bates Number
Auro-MDL 2875-0077827
Auro-MDL 2875-0077828
APL-MDL 2875-0029349
APL-MDL 2875-2854227
APL-MDL 2875-2873915
APL-MDL 2875-2672862

Amendment to Report Paragraph 59

[REDACTED]

Dated: March 4, 2022



William J. Lambert, Ph.D.